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Dual chiral silver catalyst in the synthetic approach to the core of hepatitis C virus inhibitor GSK 625433 using enantioselective 1,3-dipolar cycloaddition of azomethine ylides and electrophilic alkenes

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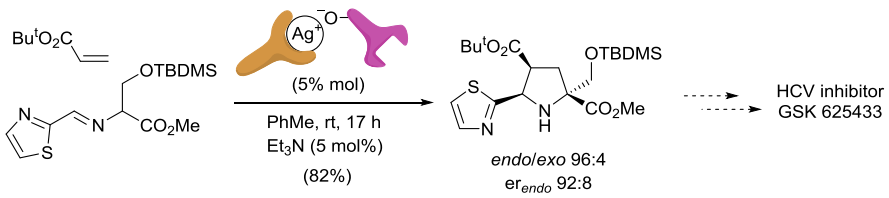
Ihssene Chabour, Luis M. Castelló, Juan Mancebo-Aracil, María Martín-Rodríguez, M. de Gracia Retamosa, Carmen Nájera,* and José M. Sansano*



Stereochemistry Abstract

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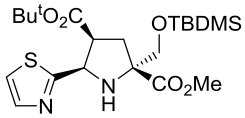

Er = 93:7
$[\alpha]_D$ = -8.0 (*c* 1, CH_2Cl_2, 93:7 er from HPLC)
Source of chirality: (S_a,*R*,*R*)-Binol derived phosphoramidite and chiral (*R*)-binol-phosphoric acid

$C_{16}H_{27}N_2O_3SSi$

4-(*tert*-Butyl) 2-methyl (2*R*,4*S*,5*R*)-2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate

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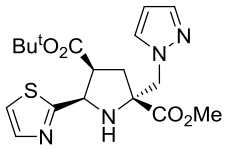

Er = 93:7
$[\alpha]_D$ = + 7.7 (*c* 0.6, $CHCl_3$, 93:7 er)
Source of chirality: (S_a,*R*,*R*)-Binol derived phosphoramidite and chiral (*R*)-binol-phosphoric acid

$C_{13}H_{15}N_4O_2S$

4-(*tert*-Butyl) 2-methyl (2*R*,4*R*,5*R*)-2-[(1H-pyrazol-1-yl)methyl]-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate

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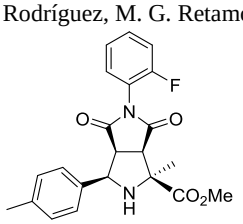

Er = 61:39%
$[\alpha]_D$ = - 3.7 (*c* 1.1, $CHCl_3$, 61:39 er from HPLC)
Source of chirality: (S_a,*R*,*R*)-Binol derived phosphoramidite and chiral (*R*)-binol-phosphoric acid

$C_{22}H_{21}FN_2O_4$
Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-(2-fluorophenyl)-1-methyl-4,6-dioxo-3-(*p*-tolyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate

Dual chiral silver catalyst in the synthetic approach to the core of hepatitis C virus inhibitor GSK 625433 using enantioselective 1,3-dipolar cycloaddition of azomethine ylides and electrophilic alkenes

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Dedicated to the memory of Prof. Howard Flack

Abstract: The asymmetric 1,3-dipolar cycloaddition (1,3-DC) of an imino ester **5** with *tert*-butyl acrylate is catalyzed by a dual chiral silver(I) complex formed from a chiral phosphoramidite **14** and the chiral silver(I) binolphosphate (*R*)-**17**. This reaction is selected to perform the synthesis of enantiomerically enriched key structure to access the third generation of GSK HCV inhibitors. The scope of this dual chiral catalytic system is analyzed employing different imino esters and dipolarophiles, and furtherly compared with the same cycloaddition reactions performed with chiral phosphoramidite **14**·Ag(I) complex.

Keywords: Cycloaddition · azomethine ylides · phosphoramidite · silver(I) · enantioselective · dual activation

1. Introduction

The enantioselective synthesis of pyrrolidines or proline derivatives constitutes a very important trend in organic chemistry due to the interest of them in many scientific fields.[1] Since the biological and medicinal point of view, molecules possessing antibiotic, antitumor, analgesic, neuroexcitatory activities, etc., have been widely described. However, the development of antiviral compounds (commercially available or in clinical survey) constitutes one of the main applications of these skeletons.[2,3] At this moment, many antiviral agents (used individually or in combination with another drugs) administrated to patients include a nitrogenated five-membered ring, for example, elbasvir, grazoprevir, velpatasvir, ombitasvir, paritaprevir, boceprevir, telaprevir and daclatasvir have been recently developed.[4] The complex skeleton of these molecules contrast with a family of prolinate derivatives **1**-**3** (Figure 1) reported by GSK through successive evolutions.[5] These compounds act as polymerase inhibitors of the several strands of the virus responsible of the Hepatitis C. Besides, less amount of effective doses and reduced secondary effects converted these products in a promising treatment for hepatitis C virus (HCV) infected people.[6,7]

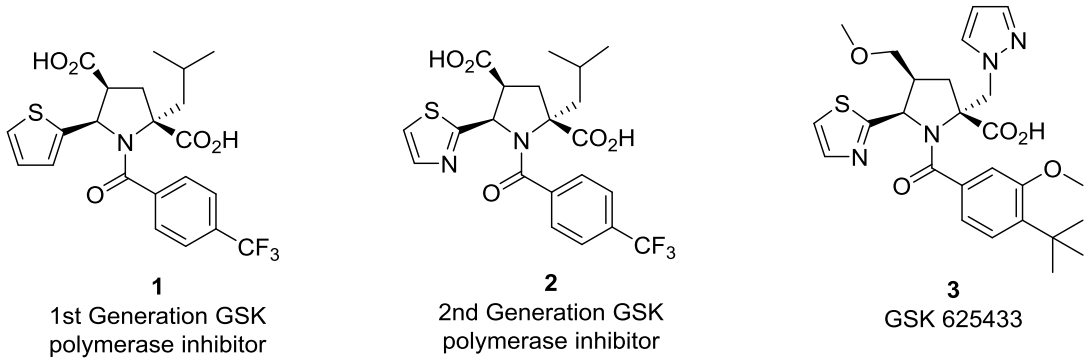
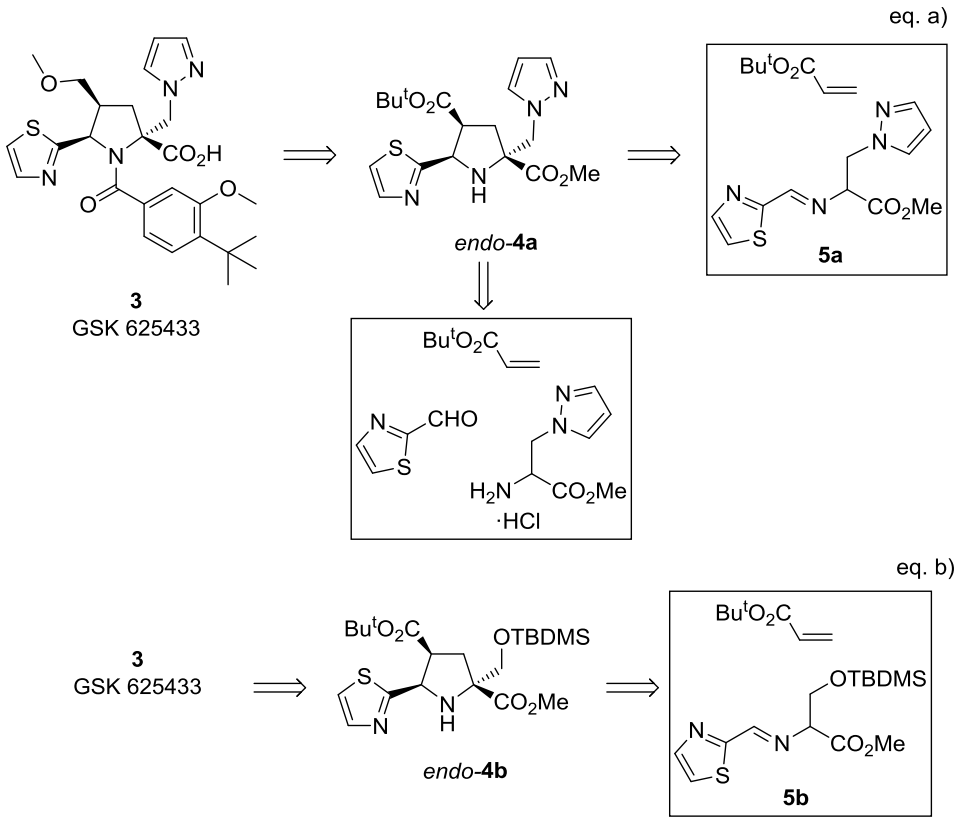


Figure 1. Family of GSK HCV inhibitors.

In our group, the asymmetric synthesis of the 1st **1**[8,9] and 2nd generation **2**[10] antiviral drugs employing diastereo-[8] and enantioselective[2,11] 1,3-dipolar cycloaddition (as key-step) between the corresponding methyl iminoleucinate and a lactate derived acrylate,[8] or this imino ester with *tert*-butyl acrylate employing a chiral phosphoramidite-$AgClO_4$ catalytic complex[8] or a chiral dimeric Binap-gold(I) complex,[10] respectively, was developed. In both routes, the overall yields obtained were moderate to good and enantioselectivities were very high, especially in the case of the 2nd generation inhibitor (99% *ee*). In this work, we report the efforts dedicated to build enantioselectively the core heterocyclic ring precursor of the GSK 625433 polymerase inhibitor **3**[12] and also a brief study of the scope and versatility of the new developed catalyst will be disclosed.

2. Results and discussion

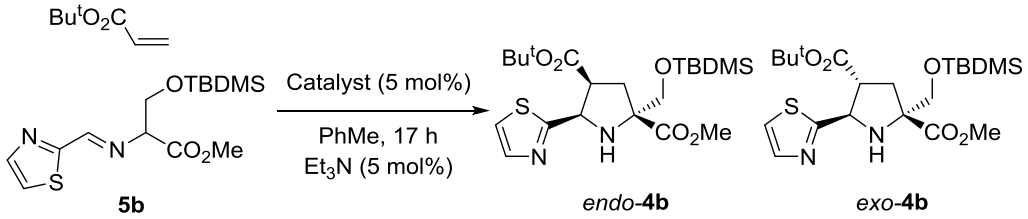
According to the classical retrosynthetic analysis of this family of compounds, we envisaged that the enantiomerically enriched cycloadducts *endo*-**4** type were the key compounds to the access to antiviral agent **3**. Initially, we designed two alternative approaches where the pyrazole ring was bonded in the starting imino ester (Scheme 1, eq. a) and a second retrosynthesis in which the pyrazole was introduced once the 1,3-DC occurred (Scheme 1, eq. b). Starting imino ester **5a** could be generated, under mild conditions, from commercially available 3-(1-pyrazolyl)-L-alanine methyl ester hydrochloride but important amounts of the product, resulting from the β-elimination of pyrazole, were detected by ^{1}H NMR spectroscopy. The non-asymmetric multicomponent 1,3-DC was then tested employing *tert*-butyl acrylate, 2-thiazolecarbaldehyde and the amino ester, furnishing the undesirable β-elimination product.[13] This problem was overcome employing the route starting from O-TBDMS serine derivative (Scheme 1, eq. b). Stable imino ester **5b** was much more appropriate to run the non-asymmetric cycloaddition and, in consequence, adequate to survey the enantioselective 1,3-DC. This imino ester **5b** was obtained, in almost quantitative yield, by reaction of 2-thiazolecarbaldehyde with the known compound O-TBDMS serine methyl ester[14] in DCM at room temperature for 19 h and it was employed in the cycloadditions without any other purification (see experimental part).

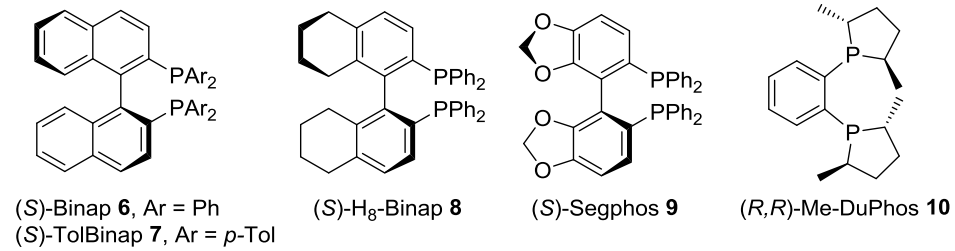


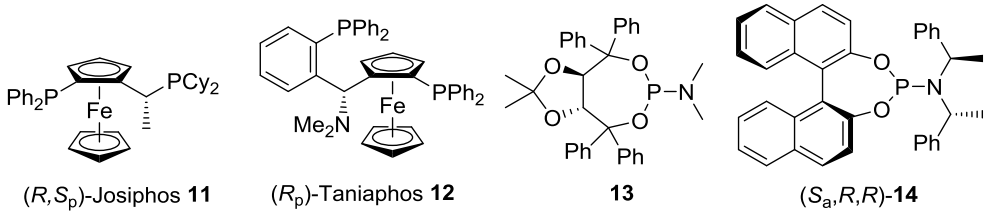
Scheme 1. Retrosynthetic analysis.

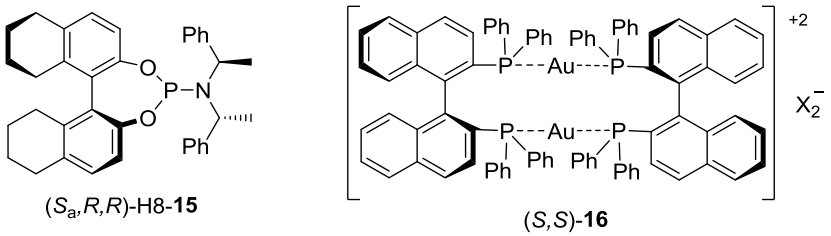
Many chiral ligands and silver salts were tested in 5 mol% loading (Scheme 2 and Table 1) but always using toluene as better solvent (not registered in Table 1). The cycloadditions performed at room temperature involving Binap **6** afforded very good conversions but with moderate enantioselections (Table 1, entries 1-3).[15] The best silver salt was $AgSbF_6$, which gave, at room temperature, the desired compound *endo*-**4b** as a 85:15 mixture of diastereoisomers in 85:15 enantiomeric ratio (Table 1, entry 2). The lowering of the temperature was not beneficial for this transformation (Table 1, entry 3).[16] Chiral ligands **7** and **8** did not improve the results achieved by Binap **6** and almost racemic compound *endo*-**4b** was isolated when AgOBz or $AgSbF_6$ were combined with chiral ligands **9**-**13** (these results are not included in Table 1). Phosphoramidite (S_a,*R*,*R*)-**14**·AgTFA complex and the analogous one formed with $AgSbF_6$ furnished identical conversions, diastereomeric and enantiomeric ratios (Table 1, entries 4 and 5). The analysis of the temperature was next studied (Table 1, entries 5-7) obtaining an increment of the diastereomeric ratio (up to 99:1, at -80 ºC) but with a moderate enantioselection (80:20 at the same temperature). Analogous H8-chiral complex **15**·$AgSbF_6$ was not suitable for inducing a very high enantiodiscrimination (Table 1, entry 8). Because of dimeric gold species (*S*,*S*)-**16**·TFA_2 was effective in the synthesis of the second generation GSK-agents it was used at 0 ºC in the cycloaddition of *tert*-butyl acrylate and imino ester **5b**. The reaction was almost complete after 48 h reaction time giving *endo*-**4b** as major diastereoisomer in 85:15 dr and modest enantioselection (78:26 er, Table 1, entry 9). (*S*,*S*)-**16**·$(OBz)_2$ catalytic complex was not effective affording lower diastereomeric and enantiomeric ratios (Table 1, entry 10). However, the dual chiral catalyst **14**·Ag-(*R*)-**17**, formed by reaction of silver carbonate and chiral (*R*)-binol-phosphoric acid in toluene[17] for

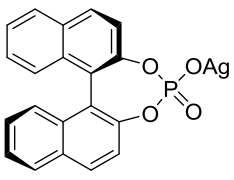
1 h followed by the addition of phosphoramidite **14**, produced at room temperature *endo*-cycloadduct **4b** in excellent conversion and high diasteromeric and enantiomeric ratio (Table 1, entry 11). A lowering of the temperature to -20 ºC did not produce any significant amelioration of the enantiomeric ratio. The corresponding enantiomer *ent-endo*-**4b** was easily obtained by employing the enantiomeric chiral catalytic system such as it is shown in entry 12 of Table 1. The configuration of these two enantiomeric forms of the dual chiral silver complex resulted to be the matched combination for this transformation because the other two detailed in the last two entries of Table 1 afforded lower enantiomeric ratios although with excellent conversions. From these three last entries, the absolute configuration induced in cycloadducts is strongly dependent of the axial chirality of the phosphoramidite ligand.











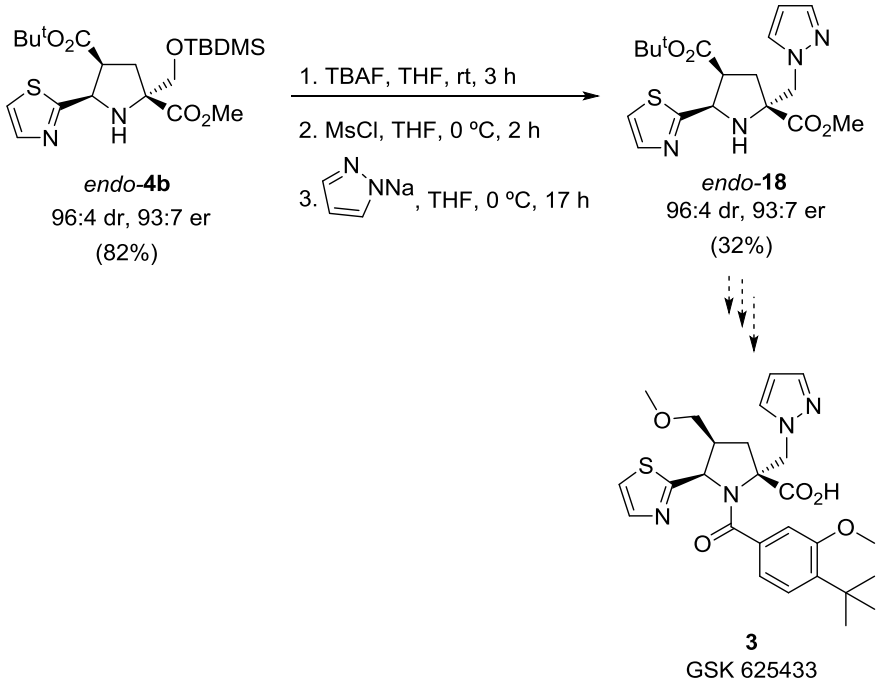
Scheme 2. Chiral ligands employed in the optimization study.

Table 1. Study of the reaction conditions for the synthesis of **4b**.

Entry	Catalyst	T (ºC)	Conv. (%)[a]	dr[a]	er[b]
1	**6**·AgTFA	25	>95	70:30	81:19
2	**6**·$AgSbF_6$	25	>95	85:15	85:15
3	**6**·$AgSbF_6$	0	>95	85:15	82:18
4	**14**·AgTFA	25	>95	90:10	66:34
5	**14**·$AgSbF_6$	25	>95	93:7	65:35
6	**14**·$AgSbF_6$	-20	>95	95:5	69:31
7	**14**·$AgSbF_6$	-80	>95	99:1	80:20
8	**15**·$AgSbF_6$	25	>95	99:1	59:31
9	**16**·$(TFA)_2$	0[c]	90	90:10	78:26
10	**16**·$(OBz)_2$	0[c]	95	85:15	76:24
11	**14**·Ag-(*R*)-**17**	25	>95	96:4	93:7
12	(R_a,*S*,*S*)-**14**·Ag-(*S*)-**17**	25	>95	95:5	8:92
13	(R_a,*S*,*S*)-**14**·Ag-(*R*)-**17**	25	>95	96:4	23:77
14	**14**·Ag-(*S*)-**17**	25	>95	90:10	75:25

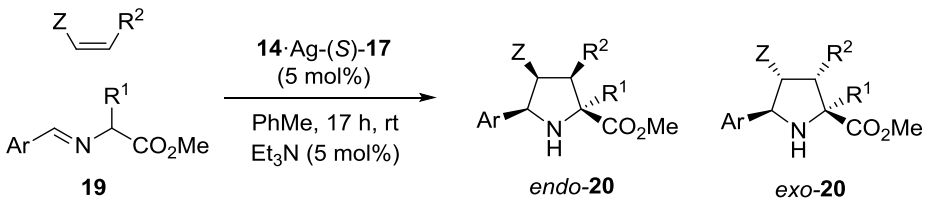
[a] Determined by ^{1}H NMR of the crude reaction mixture. 10 h Reaction time.
[b] Determined by HPLC using chiral stationary phase columns.
[c] 48 h Reaction time.

With compound *endo*-**4b** in hand (82% yield, 96:4 dr and 92:7 er) next three steps were carried out in a sequential manner (Scheme 3). First, TBDMS was removed using three equiv. of tetrabutylammonium fluoride (TBAF, 1 M solution in THF) at room temperature for 3 h. Mesylation of the alcohol in the absence of trimethylamine avoided undesirable ring expansion process and after 2 h at 0 ºC, sodium pyrazolide[18] was added at 0 ºC. Cycloadduct *endo*-**18** was isolated after flash chromatography in 32% overall yield from *endo*-**4b**. The final access to molecule **3** can be achieved following known procedures described for this family of HCV inhibitors.[6,7,19]



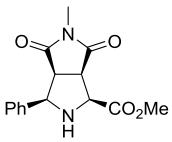
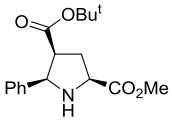
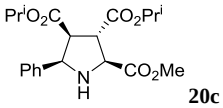
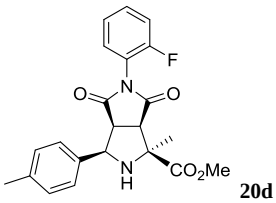
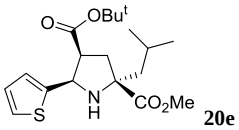
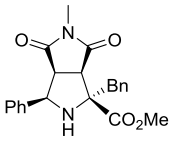
Scheme 3. Synthesis of the key enantiomer *endo*-**18** to access GSK 625433 polymerase inhibitor **3**

The determination of the absolute configuration and the scope of effectiveness of the double chiral activated complex **14**·Ag-(*R*)-**17** were studied simultaneously. Initially, *N*-methylmaleimide (NMM) was allowed to react with imino ester **19** (Ar = Ph, R^1 = H) under optimized reaction conditions yielding product **20a** (Table 2, entry 1). The absolute configuration was assigned on the basis on the comparison of its retention time (HPLC using a chiral stationary phase column) with the retention time of the identical sample isolated from the reaction catalyzed by **14**·$AgClO_4$ complex.[8] This absolute configuration was confirmed by analyzing both HPLC and specific optical rotation data of all isolated compounds described in Table 2. The dual chiral catalyst **14**·Ag-(*R*)-**17** and **14**·$AgClO_4$ chiral complex afforded similar results of **20b** and **20c** too (Table 2, entries 2 and 3). However, the presence of a substituent at the α-position of the imino ester **19** caused steric difficulties to the bulky chiral entity of **14**·Ag-(*R*)-**17**. Thus, when alanine, leucine and phenylalanine derived imino esters **19** were employed with different dipolarophiles the catalytic complex **14**·$AgClO_4$ afforded cycloadducts **20** in higher both diastereomeric and enantiomeric ratios, although chemical yields are similar using separately both catalytic complexes (Table 2, entries 4-6). It is noteworthy that compound **20d** appeared as potential novel HIV-1 integrase inhibitor,[20] and molecule **20e** is the key building block for the synthesis of the HCV inhibitor **1**.[6,8]



Scheme 4. Scope of the reaction.

Table 2. Synthesis of cycloadducts **20** in the presence of **14**·Ag-(*R*)-**17** and comparison with the results obtained employing **14**·$AgClO_4$.

					14·$AgClO_4$ (ref. 9)			**14**·Ag-(*R*)-**17**		
Ent.	R^1	Ar	Dipolarophile	Structure	Yield (%)[a]	dr[a]	er[b]	Yield (%)[a]	dr[a]	er[b]
1	H	Ph	NMM	 **20a**	80[c]	>98:2	>99:1	78[c]	>98:2	90:10
2	H	Ph	*tert*-Butyl acrylate	 **20b**	80[d]	>98:2	90:10	90[c]	>98:2	90:10
3	H	Ph	Diisopropyl fumarate	 **20c**	81[d]	>98:2	91:9	82[d]	90:10	89:11
4	Me	4-Me(C_6H_4)	*o*-FPM[e]	 **20d**	58[c]	95:5	61:39	58[c]	95:5	53:47
5	Bu^i	2-Thienyl	*tert*-Butyl acrylate	 **20e**	78[d]	>98:2	94:6	81[d]	95:5	76:24
6	Bn	Ph	NMM	 **20f**	71[f]	>98:2	95:5	67[f]	95:5	73:27

[a] Determined by ^{1}H NMR of the crude reaction mixture. 10 h Reaction time.
[b] Determined by HPLC using chiral stationary phase columns for the *endo*-stereoisomer.
[c] Reaction performed at room temperature.
[d] Reaction performed at -20 ºC.
[e] *o*-FPM = *N*-(*o*-fluorophenyl)maleimide. Compound **20d** was not prepared in ref. 9.
[f] Reaction performed at 0 ºC.

3. Conclusions

In this work, the modulation of the chiral catalyst **14**·Ag-(*R*)-**17** could be adapted to the effective approach of the imino ester and *tert*-butyl acrylate to access the enantiomerically enriched core of the antiviral agent GSK 625433 by first time. Dual chiral catalyst is very appropriate to achieve a high enantioselection in this transformation unlike to the result gave by **14**·$AgClO_4$

complex. In the case of glycine imino esters both catalysts exhibit a similar behavior in the enantioselective 1,3-DC with dipolarophiles, but for sterically hindered imino esters (derived from α-substituted amino acids) it is advisable the employment of **14**·$AgClO_4$ complex.

4. Experimental Part

4.1. General information

Melting points were determined with a Reichert Thermowar hot plate apparatus and are uncorrected. Only the structurally most important peaks of the IR spectra (recorded whit a FT-IR 4100LE (JASCO) (PIKE MIRacle ATR) are listed. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained with a Bruker AC-300 by using $CDCl_3$ as solvent and TMS as the internal standard, unless otherwise stated. Optical rotations were measured with a JASCO 2000 series. HPLC analyses were performed with a JASCO-2000 series equipped with a chiral stationary phase column (detailed for each compound in the main text) by using mixtures of *n*-hexane/isopropyl alcohol as the mobile phase at 25 ºC. Low-resolution electron impact (EI) mass spectra were obtained with a Shimadzu QP-5000 by injection or DIP, and high-resolution mass spectra were obtained with a Finnigan VG Platform or a Finnigan MAT 95S. Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates and the spots were visualized under UV light (λ = 254 nm). Merck silica gel 60 (0.040-0.063 mm) was used for flash chromatography.

4.2. Synthesis of imino ester 5b.

In a 10 mL flask was dissolved free O-TBDMS serine methyl ester[14] (357 mg, 1.5 mmol) and 2-thiazolecarbaldehyde (134 μL, 1.5 mmol) in anhydrous dichloromethane (10 mL) and magnesium sulfate (200 mg) was added. The reaction was stirred at room temperature overnight and the organic phase was washed with bine, dried and evaporated affording quantitatively the crude imine (492 mg, 1.5 mmol) as a pale yellow oil; IR (neat) ν_{max} 1743 cm^{-1}; ^{1}H NMR δ_H: 0.01, 0.05 (2s, 6H, 2xMeSi), 0.85 (s, 9H, Me_3C), 3.77 (s, 3H, MeO), 3.94 (dd, *J* = 10.5, 7.9 Hz, 1H, CH_2O), 4.16 (dd, *J* = 10.5, 5.3 Hz, 1H, C*H*CO_2Me), 4.26 (dd, *J* = 7.9, 5.3 Hz, 1H, CH_2O), 7.47, 7.93 (2d, *J* = 3.1, 2H, HC=CH), 8.48 (s, 1H, HC=N); ^{13}C NMR δ_C: -5.4, -5.3 (Me_2Si), 18.2 (*C*Me_3), 25.8 (C*C*H_3), 52.3 (OMe), 63.5 (CH_2), 74.1 (CHCO), 122.1 (CHN), 144.8 (CHS), 158.4 (CNS), 166.3 (C=N), 170.1 (CO); MS (EI-GC) *m/z*: 328 (M^+, 1%), 271(80), 241 (11), 211 (13), 165 (42), 137 (100), 89 (51), 75 (77); HRMS calculated for $C_{20}H_{24}N_2O_3SSi$: 328.1277, found: 328.1266.

4.3. General procedure for the enantioselective 1,3-DC using dual catalyst 14·Ag-(*R*)-17. Synthesis of compounds *endo*-4b and 20.

In a 10 ml vial covered by aluminum foil, Ag_2CO_3 (2.8 mg, 0.01 mmol), (*R*)-Binol-phosphoric acid (7 mg, 0.02 mmol) and toluene (3 mL) were added and the resulting mixture was stirred at room temperature for 1 h. Phosphoramidite (S_a,*R*,*R*)-**14** (10.8 mg, 0.02 mmol) was added and the reaction stirred for additional 40 min. Then, the imino ester (0.4 mmol), the dipolarophile (0.4 mmol) and triethylamine (3 μL, 0.02 mmol) were added in this order and the reaction stirred at room temperature. The mixture was cooled at -10 ºC and the amino ester **2c** (193 mg, 1 mmol), the corresponding maleimide **3** (1 mmol), and ethyl glyoxylate **1** (*ca.*50% solution in toluene, 102 μL, 1.2 mmol) were slowly added in this order. The reaction was stirred for 17 h. The solvent was evaporated and the crude product was purified purified by flash chromatography (*n*-hexane:EtOAc), affording cycloadducts *endo*-**4b** and **20**.

4.4. 4-(*tert*-Butyl) 2-methyl (2*R*,4*S*,5*R*)-2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate (*endo*-4b).

Sticky pale yellow oil, 119 mg (82%); $[\alpha]_D^{20} =$ -8.0 (*c* = 0.8, CH_2Cl_2) for 93:7 er by HPLC (Chiralpak AD-H), *n*-hexane/*i*-PrOH: 90/10, (0.7 mL/min, λ 250 nm), t_{may} = 8.3 min, t_{min} = 9.2 min; IR ν_{max}: 3345, 1727, 1677 cm^{-1}; ^{1}H RMN δ_H: 0.05, 0.09 (2s, 6H, Me_2Si), 0.87 (s, 9H, Me_3C), 1.19 (s, 9H, CO_2CMe_3), 2.16 (dd, *J* = 13.7, 8.1 Hz, 1H, CO_2MeCC*H*), 2.80 (dd, *J* = 13.7, 8.3 Hz, 1H , CO_2MeCC*H*), 3.00 (br. S, 1H, NH), 3.40 (ddd, *J* = 8.3, 8.1, 7.5 Hz, 1H, CHCO_2*t*Bu), 3.64 (d, *J* = 9.5 Hz, 1H, CH_2OTBDMS), 3.72 (s, 3H, CO_2Me), 3.79 (d, *J* = 9.5 Hz , 1H, CH_2OTBDMS), 4.93 (d, *J* = 7.5 Hz , NHC*H*), 7.24, 7.68 (2sd, *J* = 3.3 Hz,

2H, HC=CH); ^{13}C RMN δ_C: -5.6, -5.4 (Me_2Si), 18.2 (Si*C*Me$_3$), 25.8 (SiC*Me*$_3$), 27.7 (OC*Me*$_3$), 33.6 (C*C*H$_2$C), 49.5 (*C*HCO$_2$*t*Bu), 52.3 (CO$_2$*Me*), 61.5 (CHNH), 69.1 (CH$_2$OSi), 70.1 (*C*CO$_2$Me), 80.9 (O*C*Me$_3$), 118.9 (CHS), 142.3 (*C*HNCSTh), 170.3 (NCS), 171.5, 174.6 (2xCO$_2$); MS (ESI) *m/z*: 456 (M^+, 2%); HRMS for $C_{21}H_{36}N_2O_5Si$ required: 456.2112; found: 456.2108.

4.5. Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (20a):[9,21] 90 mg, 78%; $[\alpha]_D^{20} = +62.0$ (*c* 1, CH_2Cl_2) for 90:10 er, $[\alpha]_D^{20} = +61.0$ (*c* 1.18, CH_2Cl_2) for 90:10 er.[21]

4.6. 4-(tert-Butyl) 2-methyl (2*S*,4*S*,5*R*)-5-phenylpyrrolidine-2,4-dicarboxylate (20b):[9,22] 84 mg, 90%; $[\alpha]_D^{20} = +22.5$ (*c* 1.3, CH_2Cl_2) for 90:10 er, $[\alpha]_D^{20} = -26.8$ (*c* 1.3, CH_2Cl_2) for 3:97 er (opposite enantiomer).[22]

4.7. 3,4-Diisopropyl 2-methyl (2*S*,3*S*,4*S*,5*R*)-5-phenylpyrrolidine-2,3,4-tricarboxylate (20c):[9] 66 mg, 82%; $[\alpha]_D^{20} = +30.9$ (*c* 0.5, $CHCl_3$) for 89:11 er, $[\alpha]_D^{20} = +32.5$ (*c* 0.5, $CHCl_3$) for 91:9 er.[9]

4.8. Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-(2-fluorophenyl)-1-methyl-4,6-dioxo-3-(*p*-tolyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (20d): pale yellow oil, 92 mg, 58%. $[\alpha]_D^{20} = -3.5$ (*c* 1.1, $CHCl_3$) for 61:39 er by HPLC (Chiralpak OD-H), *n*-hexane/*i*-PrOH: 50/50, (1 mL/min, λ 250 nm), t_{may} = 9.7 min, t_{min} = 14.7 min; IR ν_{max}: 3370, 1771, 1690 cm^{-1}; ^{1}H RMN δ_H: 1.69 (s, 3H, MeCN), 2.32 (s, 3H, *Me*C$_6$H$_4$), 3.53 (d, *J* = 8.5 Hz, 1H, C*H*CMe), 3.40 (br. S, 1H, NH), 3.77 (dd, *J* = 10.0, 8.5 Hz, 1H, C*H*CHN), 3.87 (s, 3H, OMe), 4.92 (d, *J* = 10.0 Hz, 1H , CHN), 7.15-7.45 (m, 8H, Ar*H*); ^{13}C RMN δ_C: 22.3 (MeC$_6$H$_4$), 28.6 (*Me*CN), 49.7,51.8 (2xCHCO), 52.4 (CO$_2$*Me*), 59.2 (*C*NMe), 64.0 (NHC*H*), 126.6, 126.8, 127.3, 127.4, 128.1, 128.4, 128.6, 128.7, 129.0, 137.8 (Ar*C*), 169.1, 170.3, 172.0 (3xCO); MS (EI) *m/z*: 395 (M^+-1, 2%), 337 (45), 205 (100), 172 (18), 157 (10), 145 (70), 104 (10); HRMS for $C_{22}H_{21}FN_2O_4$ – H (M^+-1) required: 395.1407; found: 395.1403.

4.9. 4-(*tert*-Butyl) 2-methyl (2*S*,4*S*,5*R*)-2-isobutyl-5-(thiophen-2-yl)pyrrolidine-2,4-dicarboxylate (20e):[9] 95 mg, 81%; $[\alpha]_D^{20} = +23.2$ (*c* 1, $CHCl_3$) for 76:24 er, $[\alpha]_D^{20} = +38.6$ (*c* 1, $CHCl_3$) for 94:6 er.[9]

4.10. Methyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (20f):[9] 101 mg, 67%; $[\alpha]_D^{20} = -35.2$ (*c* 0.8, $CHCl_3$) for 73:27 er, $[\alpha]_D^{20} = -74.2$ (*c* 0.8, $CHCl_3$) for 95:5 er.[9]

4.11. Synthesis of 4-(*tert*-Butyl) 2-methyl (2*R*,4*S*,5*R*)-2-[(1*H*-pyrazol-1-yl)methyl]-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate (*endo*-18).

Compound *endo*-**4b** (264 mg, 0.58 mmol) was dissolved in anhydrous in THF and tetrabutylammonium fluoride (1M solution in THF) was added (1.75 mL, 1.75 mmol) at 0 ºC, and the reaction was stirred at room temperature for three hours. The solvent was evaporated and ethyl acetate (10 mL) was added. The resulting solution was washed with bine, died and evaporated affording the intermediate alcohol, which was dissolved in anhydrous THF (5 mL). This new solution was cooled at 0 °C, triethylamine (89 µL, 0.64 mmol) was added and methanesulfonyl chloride was slowly introduced (54 µL, 0.64 mmol) and stirring continued for two hours at the same temperature. At this moment, a 1:1 anhydrous DMF:THF solution (3 mL) containing sodium pyrazolide [1.75 mmol, obtained by mixing pyrazole (118 mg, 1.75 mmol) with sodium hydride (95%, 42 mg, 1,75 mmol)] was added and the reaction stirred at room temperature for 24 h. The solvent was evaporated and the residue purified by flash chromatography (*n*-hexane:EtOAc), affording cycloadduct *endo*-**18** as a pale yellow oil (70 mg, 32% overall yield). $[\alpha]_D^{20} = +7.7$ (*c* 0.6, $CHCl_3$) 93:7 er; IR ν_{max} 3065, 1728 cm^{-1}; ^{1}H NMR δ_H: 1.44 (s, 3H, C*Me*$_3$), 2.10 (dd, *J* = 10.8,

8.8 Hz, 1H, CCH_2C), 2.58 (dd, *J* = 13.0, 8.8 Hz, 1H, CCH_2C), 3.15 (m, 1H, CHCO), 3.65-372 (m with s at 3.73, 5H, NH, CH_2N, OMe), 3.86 (d, *J* = 10.6 Hz, 1H, CH_2N), 4.86 (d, *J* = 8.5 H, 1H, H, CHN), 7.26 (m, 3H, CHCHNN, CHS), 7.64 (m, 2H, 2xC=CHN); ^{13}C NMR δ_C: 27.9 (CMe_3), 29.7 (CCH_2C), 52.1 (*C*HCO), 52.3 (OMe), 62.5 (CHNH), 67.3 (CH_2N), 70.2 (N*C*CO), 81.3 (CMe_3), 100.0 (*C*HCHNN), 119.1 (CHS), 128.1 (CHNN), 129.1 (CHNN), 142.5 (*C*HNCS), 171.5, 171.6, 174.5 (NCS, 2xCO); MS (EI-GC) *m/z*: 392 (M^+, 5%), 383 (10), 343 (15), 311 (24), 255 (100), 86 (13), 73 (13); HRMS calculated for $C_{18}H_{24}N_4O_4S$: 392.1518, found: 392.1509.

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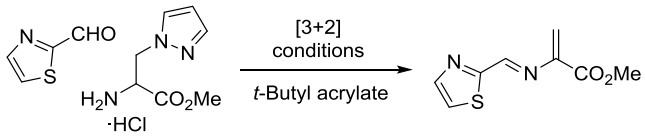

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